REMARKS

Claims 15-30 are pending in the application. Claims 15-18 and 27-30 have been withdrawn from consideration, with claims 19-26 remaining.

Applicants have now canceled claim 22. Applicants have amended claims 19-20 to depend from claim 24, rather than the canceled claim 1. Applicants have also amended claims 24-26 to recite "an isolated DNA" and to remove recitation of the terms "functional fragments" and "functional derivatives".

Applicants have amended claim 23 to recite steps of the method. Support for this amendment is found in the specification, at page 8, which describes a method for identifying, isolating and cloning one of the DNA fragments and a method for identifying DNA fragments involved in the biosynthesis of ansamycins.

Applicants have amended claim 24 to remove recitation of the term "least 15 consecutive nucleotides" and to instead recite that the claimed isolated DNA fragment "has 90% or greater sequence homology to a region of SEQ ID NO 3" and "encodes one or more of the proteins or polypeptides having a rifamycin biosynthesis enzymatic function possessed by a rifamycin biosynthesis protein selected from the group consisting of the proteins encoded by ORF A, B, C, D, E and F of the *Amycolatopsis mediterranei* rifamycin synthesis gene cluster." Support for this amendment is found in the specification, at page 3, second and third paragraphs. Additional support for this amendment is found in the specification, at page 6, lines 15-25, and at page 7, line 3 to the end of the page.

Accordingly, these amendments add no new matter.

35 U.S.C. § 101 – Statutory Subject Matter

The Examiner has rejected claims 22 and 24-26 as allegedly directed to non-statutory subject matter. The Examiner has suggested that an amendment to include the phrase "An isolated DNA fragment" would be remedial. Applicant thanks the Examiner for this suggestion and has amended claims 22 and 24-26 accordingly. This rejection is now moot and should be withdrawn.

35 U.S.C. § 102 - Anticipation

The Examiner has rejected claims 22 and 24 as allegedly anticipated by Donadio et al., Science 252: 675-679 (1991). The Examiner alleges that *Donadio* discloses a DNA fragment comprising at least 15 consecutive nucleotides which are the same as 15 consecutive nucleotides from SEQ ID NO: 3 of the present patent application. Applicants have amended claim 24 to remove

recitation of the 15 consecutive nucleotides. Applicants have also canceled claim 22. Accordingly, this rejection is now moot and should be withdrawn.

The Examiner has rejected claims 22 and 24 as allegedly anticipated by U.S. Pat. No. 5,763,569 to Brown *et al.* The Examiner alleges that *Brown* discloses a DNA fragment comprising at least 15 consecutive nucleotides which are the same as 15 consecutive nucleotides from SEQ ID NO: 3 of the present patent application. Applicants have amended claim 24 to remove recitation of the 15 consecutive nucleotides. Applicants have also canceled claim 22. Accordingly, this rejection is now moot and should be withdrawn.

35 U.S.C. § 112, First Paragraph – Written Description

The Examiner has rejected claims 25 and 26 as allegedly not sufficiently described in the specification so as to show possession of the claimed invention. The Examiner alleges that the specification does not provide a detailed chemical structure of the claimed nucleotides, with the exception of ORF, A, B, C, D, E and F of SEQ ID NO: 3 or one or more of the proteins or polypeptides depicted in SEQ ID NOS 4 to 9. Applicants respectfully traverse.

As amended, claims 25 and 26 recite only ORF, A, B, C, D, E and F of SEQ ID NO: 3 or one or more of the proteins or polypeptides depicted in SEQ ID NOS 4 to 9. Recitation of the term "functional fragment" has been removed. Accordingly this rejection is now moot as to claims 25 and 26.

As to claim 24 as currently amended, the claim recites both structural and functional elements, together providing a description of the claimed nucleotides. The specification provides support for both elements.

Structurally, the claims recite sequence homology to the nucleotide sequence provided in the specification. The specification also describes how to address structural variance within the scope of the claimed sequence homology on page 7, fifth paragraph.

> Structural differences can be regarded as minimal as long as there is a significant overlap or similarity between the various sequences, or they have at least similar physical properties. The latter include, for example, the electrophoretic mobility, chromatographic similarities, sedimentation coefficients, spectrophotometric properties etc. In the case of nucleotide sequences, the agreement should be at least 70%, but preferably 80% and very particularly preferably 90% or more. In the case of the amino acid sequence, the corresponding figures are at least 50%, but preferably 60% and particularly preferably 70%. 90% agreement is very particularly preferred.

Functionally, the claims recite that the fragment encodes a polypeptide having a rifamycin biosynthesis enzymatic function. As stated in the specification, page 6, lines 15-18:

> Examples of what is meant by enzymes or enzymatically active domains involved in this biosynthesis are those necessary for synthesizing, starting from 3-amino-5-hydroxybenzoic acid, the ansamycins such as rifamycin, for example polyketide synthases, acyltransferases, dehydratases, ketoreductases, acyl carrier proteins or ketoacyl synthases.

Additional description of the steps involved in rifamycin biosynthesis is provided in the specification, page 3, second paragraph:

> Starting from [3-amino-5-hydroxybenzoic acid], which is presumably activated as coenzyme A, the entire aliphatic bridge is synthesized by a multifunctional polyketide synthase, The length of the bridge and the processing of the keto groups, which are initially formed by the condensation steps, are controlled by the polyketide synthase. To build up the complete aliphatic bridge for rifamycins, 10 condensation steps, 2 with acetate and 8 with propionate as building blocks, are necessary. The sequence of these individual condensation steps is likewise determined by the polyketide synthase. Structural comparisons and studies with incorporation of radioactive acetate and propionate have shown that the sequence of acetate and propionate incorporation for the various ansamycins takes place in accordance with a scheme which appears to be identical or very similar in the first condensation steps. Thus, from a common synthesis scheme of the ansamycin polyketide synthases (the rifamycin synthesis scheme), the syntheses of the various ansamycins sooner or later branch off, in accordance with their structural difference from the rifamycin structure, into side branches of the synthesis (Ghisalba et al., Biotechnology of Industrial Antibiotics Vandamme E. J. Ed., Decker Inc. New York, (1984) 281-327).

The specification also describes how to address the function of the encoded polypeptides within the scope of the claimed sequence, as described on page 7, fourth paragraph:

> Functional differences can be regarded as minimal if, for example, the nucleotide sequence coding for a polypeptide, or a protein sequence has essentially the same characteristic properties as the initial sequence, whether in respect of enzymatic activity, immunological reactivity or, in the case of a nucleotide sequence, gene regulation.

Additional information is presented elsewhere in the specification. Using this information, one of skill in the art at the time the application was filed would have understood that the inventors had conceptual possession of a DNA fragment having the structural and functional properties recited in claim 24. Accordingly, the specification provides a written description of claim 24 and the dependent claims 25-26.

Applicants respectfully request that this rejection be withdrawn.

35 U.S.C. § 112, First Paragraph – Enablement

The Examiner has rejected claims 19-22 and 24-26 as allegedly not enabled for the recitation of functional fragments of the disclosed nucleotide sequences. Applicants have amended the claims to remove recitation of the term "functional fragments". Accordingly, this rejection is now moot and should be withdrawn.

35 U.S.C. § 112, Second Paragraph - Definiteness

The Examiner has rejected claims 19-23 as allegedly indefinite for dependence on canceled claim 1. Applicants have amended claims 19, 20 and 22 to recite that the claims depend from claim 24. Accordingly, this rejection is now moot and should be withdrawn.

The Examiner has rejected claim 23 as allegedly indefinite for not providing any steps in the method of using the hybridization probe. Applicants have amended claim 23 to add a method step. Accordingly, this rejection is now moot and should be withdrawn.

The Examiner has rejected claim 24 as allegedly indefinite for the recitation of "the DNA region involved in the gene cluster" and for the recitation of a sequence "which is" SEQ ID NO 1 or SEQ ID NO 3. Applicants have amended claim 24 to remove recitation of these terms. Accordingly, this rejection is now moot and should be withdrawn.

The Examiner has rejected claim 25 as allegedly indefinite for the recitation of "said fragment comprises a nucleotide sequence selected from the group consisting of ORF A, B, C, D, E, F, and functional fragments thereof, or encodes one or more of the proteins or polypeptides, or functional derivatives thereof". Applicants have amended claim 25 to remove recitation of these terms. Accordingly, this rejection is now moot and should be withdrawn.

The Examiner has rejected claim 26 as allegedly indefinite for the recitation of "wherein said fragment comprises a nucleotide sequence which is ORF A, or functional derivatives thereof, depicted in SEQ ID NO 4". Applicants have amended claim 25 to remove recitation of this term. Accordingly, this rejection is now moot and should be withdrawn.

In view of the foregoing, Applicant submits the application is now in condition for allowance and respectfully requests early notice to that effect. Should the Examiner have any questions, please contact the undersigned attorney.

Respectfully submitted,

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